Are We Missing Vitamin B_{12} Deficiency in the Primary Care Setting?

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ABSTRACT

Vitamin B_{12} deficiency is present in 5% to 20% of the elderly population and may begin in middle age, although there is a paucity of research to demonstrate this suspicion. One common cause, malabsorption, is affected by many factors often seen in the primary care setting, including prolonged use of proton pump inhibitors or metformin or as a result of gastric bypass surgery. The traditional sign of B_{12} deficiency, macrocytic anemia, can be masked by the folic acid supplementation in all enriched cereals/grains mandated by the US Food and Drug Administration since 1998. Vitamin B_{12} deficiency causes neurologic deficits that significantly impact quality of life and other conditions and is therefore worthy of recognition and treatment.

Keywords: B_{12} deficiency, B_{12} supplementation, masking by folic acid supplementation, methylmalonic acid, neurologic impairment

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INTRODUCTION

We were all educated to consider vitamin B_{12} deficiency as part of a differential when evaluating a patient for macrocytic anemia. Additionally, we have all had elderly patients in our offices requesting B_{12} injections during routine visits to "give them energy." B_{12} deficiency is well recognized in the geriatric population, with a prevalence of 5% to 20%.[1] Increasing age is independently associated with poor nutritional status, which may partly explain the poor clinical outcome in older patients.[2] However, have we stopped to consider that we might be missing B_{12} deficiency in our normocytic middle-aged and older

patients? Routine screening practices rarely result in findings of macrocytic anemia in this age group, yet two recent cases have caused me to consider B_{12} deficiency as a differential, and research of the subject has confirmed that I have reason to be suspicious.

CASE 1

MH was a 48-year-old female who recently survived a life-threatening methicillin-resistant *Staphylococcus aureus* infection of her abdomen that required a prolonged intensive-care unit stay after what was supposed to be a minor laparoscopic procedure. She presented 6 weeks after hospital discharge, eating well, sleeping well, and yet thoroughly exhausted, weak, and wondering how she was going to return to teaching in the next month. Having recently read about B_{12} function in the body and recognizing that it is in high demand during times of rapid cell turnover, I checked MH's B_{12} level as well as her methylmalonic acid (MMA) level and, sure enough, she was deficient, even though she was not anemic. After a month's course of supplementation, she was largely back to "normal" and was able to return to teaching.

CASE 2

A 55-year-old patient survived a severe subarachnoid hemorrhage with minimal neurologic deficit. He was well screened and cared for by his family physician, including recent normal laboratory results. Four months out, he was back to work but only able to manage half days because of persistent fatigue. He struggled with mild short-term memory loss. Not being his health care provider, I was not in a position to test him for B_{12} deficiency; recognizing that he had been through weeks of bed rest and therefore significant cell turnover, I recommended he start high-dose oral B_{12} supplementation (2,000 mcg per day). Within 2 weeks, he was able to get through full days of work without fatigue and found that his memory had returned to near normal.

These cases stand out because of the dramatic events that preceded their presentations as well as the prompt response they each experienced upon supplementation. Research of this subject has since revealed that there are many more subtle presentations of B_{12} deficiency, as well as many causative factors that are common in our society today.

PHYSIOLOGY OF VITAMIN B_{12}

Vitamin B_{12}, also known as cobalamin, is crucial for DNA synthesis in cells undergoing rapid turnover, such as hematopoietic and enteric lining cells. It is also vital to optimal function of the immune system. B_{12} is stored in the liver, but it can take 5 to 10 years for a person to become B_{12} deficient due to malabsorption; however, demand for B_{12} markedly increases during times of physical stress, which depletes stores as well. The body does not synthesize B_{12}; we rely on exogenous sources of meat and dairy products to meet our needs. Unless someone is a strict vegetarian, the typical American diet has sufficient B_{12} to meet recommended daily allowance (RDA) standards, presuming normal absorption. Active absorption of B_{12} is a complex process and not fully understood. Upon ingestion, B_{12} requires an acidic stomach as well as intrinsic factor, secreted by gastric parietal cells, to be absorbed in the terminal ileum.[3] Passive absorption also occurs in the small bowel.

Other neurological symptoms of B_{12} deficiency include memory loss, irritability, and dementia.

SIGNS AND SYMPTOMS OF B_{12} DEFICIENCY

B_{12} deficiency traditionally causes macrocytic anemia but can be present in normocytic patients.[1] Neurologic deficits are a common result of B_{12} deficiency; indeed, a recent study demonstrated neurologic deficits were more common than anemia and demonstrable with neuroelectric physiological studies.[4] These deficits are due to abnormal synthesis of myelin protein, causing demyelination of the dorsal and lateral columns of the spinal cord. Symptoms include paresthesias of the lower extremities, disequilibrium, and loss of vibratory sensation.[3,5] These symptoms are symmetric, more common in the lower extremities than upper, and increase the risk of falling in all age groups.[4] Other neurological symptoms of B_{12} deficiency include memory loss, irritability, and dementia caused by axonal degeneration in the central nervous system.[6] B_{12} deficiency has been shown in vitro to increase osteoclast activity, thus contributing to decreased bone

health and increased risk of fracture.[7] Other B_{12} deficiency symptoms include glossitis (swollen, beefy red tongue), vaginal atrophy, and mild diarrhea. "The dietary deficiency or anemia of chronic diseases should be suspected in every case of glossitis, glossodynia, angular cheilitis, erythematous mucositis, oral candidosis, recurrent oral ulcer, and burning mouth when no other obvious causes are found."[8] Micronutrient-deficient states, including B_{12} deficiency, have been linked to cardiovascular disease and cancer, though cause and effect are not clear.[2,4] A 2005 case study describes a patient with chronic erythema nodosum who experienced complete resolution of symptoms after 2 weeks of parenteral B_{12} supplementation, leading the author to recommend screening patients with this condition.[10]

FOLIC ACID SUPPLEMENTATION MASKING B_{12} DEFICIENCY

Folic acid works in conjunction with B_{12} for DNA synthesis. Folic acid deficiency causes macrocytic anemia but never neurologic deficits. Common causes of folic acid deficiency include poor diet and alcoholism. Since January 1998, the US Food and Drug Administration has required all enriched cereal/grain products to be fortified with folic acid, with the goal of reducing neural tube congenital defects.[10] Nutritionists have expressed concerns that folic acid fortification masks B_{12} deficiency, and a 2007 study demonstrated cognitive impairment in patients with high folate status in the presence of low B_{12}. These patients were anemic without macrocytosis.[10] The authors suggest that excess folic acid precipitates both hematologic and neuropsychiatric manifestations of B_{12} deficiency. Interestingly, folic acid conferred cognitive protection in the presence of normal B_{12} levels. The point here is that folic acid supplementation in the presence of B_{12} deficiency may actually aggravate neurological symptoms.

CHRONIC USE OF PPIS INCREASING B_{12} DEFICIENCY?

Food malabsorption causes 60% to 70% of B_{12} deficiency.[11] One of the most common causes of malabsorption is gastric atrophy, which is present in 5% to 20% of the elderly population, due to aging.[1] However, B_{12} deficiency is increasingly linked to prolonged use of proton pump inhibitors (PPIs), which decrease the acidity of the stomach environment and thereby impede B_{12} absorption.[12] Given that a large percentage of our population is taking PPIs and that PPIs are now readily available without a prescription, the risk for B_{12} deficiency due to chronic PPI use is increased.

B_{12} DEFICIENCY IN THE PRESENCE OF OBESITY

It is well known that our country is suffering an epidemic of obesity. While obesity itself does not contribute to vitamin deficiency, the consequences of obesity can play a role. One intervention for obesity that is recognized by Medicare is gastric bypass surgery. During this procedure, a significant portion of the stomach is removed, with the resultant loss of parietal cells. This decreases the amount of intrinsic factor available to facilitate absorption of vitamin $B_{12.}$[6,13] This is not to be confused with pernicious anemia, which is thought to be an autoimmune disorder that causes gastric atrophy, also resulting in insufficient intrinsic factor and thus causing B_{12} deficiency.[11]

Type 2 diabetes mellitus is a complication of obesity, and first-line pharmacologic therapy is metformin. Metformin affects the absorption of vitamin B_{12} in the ileum by antagonizing the calcium-dependent ileal membrane; consequently, it is estimated that 10% to 30% of patients taking metformin are B_{12} deficient.[14] Interestingly, B_{12} deficiency is best managed in this scenario by supplementation with oral calcium, which overrides metformin's antagonizing properties and allows B_{12} absorption in the ileum.[14]

B_{12} DEFICIENCY AFTER PROLONGED OR CRITICAL ILLNESS

As the two cases described above suggest, prolonged or critical illness, with its massive demands on the body's metabolism, is an often unrecognized cause of B_{12} deficiency.[15] Any patient recovering from a critical illness, regardless of age, deserves screening with B_{12} and MMA levels. Additionally, B group vitamin supplementation immediately postinfarct may have antioxidant and antiinflammatory effects in stroke disease.[16]

B_{12} DEFICIENCY CAUSED BY SMALL BOWEL DISEASE

B_{12} deficiency is common in both celiac disease[17] and Crohn's disease, particularly if the patient has had an ileal or ileocolonic resection.[18] As described above, B_{12} is absorbed in the terminal ileum, an area commonly involved in Crohn's disease. It is not as clear why B_{12} deficiency is found in patients with celiac disease, which is a disorder of the proximal small bowel. The

association with celiac, an autoimmune disease, is separate from autoimmune pernicious anemia.[18] It is important to routinely screen patients with small bowel disease for B_{12} deficiency.

B_{12} DEFICIENCY IN PATIENTS DIAGNOSED WITH HIV

Patients diagnosed with human immunodeficiency virus (HIV) infection are at increased risk of B_{12} deficiency, thought to be due to poor nutrition and/or chronic diarrhea, among other factors. Studies estimate that between 10% and 39% of HIV-infected patients are B_{12} deficient and would benefit from supplementation, especially given the role of B_{12} in the immune system.[3]

APPROPRIATE LABORATORY SCREENING

Serum vitamin B_{12} levels have a wide range of normal, with a low reference range of 200 to 220 pg/mL.[19] MMA, a substance produced when amino acids break down, is elevated in the presence of B_{12} deficiency, even when serum B_{12} levels are in the low to normal range. MMA concentration is considered to be a sensitive and specific diagnostic tool, particularly helpful in identifying preclinical or subtle cases of B_{12} deficiency.[10] MMA level rises when B_{12} levels are less than 400 pg/mL.[20] Caution should be used when interpreting results in the presence of renal insufficiency, which also raises MMA levels.[10] Elevated MMA levels are independently associated with cognitive decline, specifically with lower scores in language comprehension and expression.[21] Homocysteine levels may be elevated in vitamin B_{12}-deficient states as well as when folic acid is low, but MMA is only elevated with low B_{12}. It is reasonable and appropriate to screen patients with serum B_{12}, folic acid, and MMA levels.

WHO TO SCREEN

I assert that we nurse practitioners should not wait for macrocytic anemia to appear before screening patients for B_{12} deficiency; indeed, in light of folic acid fortification, any patient with normocytic anemia should be screened for B_{12} deficiency.[10] In addition to all elderly patients, others who would be appropriate for screening include type 2 diabetics receiving metformin, patients taking prolonged PPI therapy, patients who have been through excessive physical stress, ie, critical illness, and patients complaining of imbalance or decreased sensation in lower extremities. Patients diagnosed with celiac or Crohn's diseases require routine screening. Additionally patients presenting with oral ulcers, tongue complaints, or persistent mild diarrhea should be screened. All patients presenting with complaints of memory loss and perhaps those with persistent irritability should be screened as well. Patients with autoimmune disorders have a higher prevalence of B_{12} deficiency than the general population and thus should be screened as well.[22]

SUPPLEMENTATION

Prior to initiating B_{12} supplementation in patients found to be deficient, it is crucial to rule out any causative factors, so that the underlying cause may be addressed. It is tempting to recommend taking daily vitamin B_{12} to all patients, as the risk of toxicity is extremely low.[19] However, it seems an unnecessary expense for healthy patients, and research is lacking to demonstrate clear benefit.[23] Thus, for all patients, education is in order to ensure adequate intake of dietary B_{12}, including fortified cereals as well as meat and dairy products. It would be reasonable to begin daily supplementation of B_{12}, 1,000 to 2,000 mcg per day, for patients with B_{12} levels less than 400 pg/mL, since that is the level at which MMA levels begin to rise. For symptomatic patients in whom B_{12} deficiency is established, especially those with neurologic symptoms, prognosis depends on prompt recognition and treatment.[3,24] Three routes of B_{12} supplementation are available: parenteral, nasal, and oral. Traditionally, supplementation in the primary care setting has been parenteral, but this is no longer necessary. It is sufficient to supplement orally with high doses of vitamin B_{12}, 1,000 to 2,000 mcg per day.[25] Even for patients diagnosed with pernicious anemia and therefore unable to actively absorb B_{12}, passive absorption in the small bowel enables an absorption rate of 1%. Thus, supplementation with 1,000 mcg per day will give that patient 10 mcg, substantially more than the RDA of 2.4 mcg/day.[26]

Prescription B_{12} nasal gel is expensive and need be given only to patients with pernicious anemia who have persistent low-serum B_{12} and elevated MMA after oral supplementation. Patients presenting with significant neurological symptoms (i.e., burning feet) may respond more rapidly to initial parenteral supplementation followed by oral supplementation,[9] and there is an increased reliance on patient compliance with oral supplementation. For patients who are not B_{12} deficient, supplemen-

tation with a multivitamin formulated at about 100% RDA can decrease the prevalence of suboptimal vitamin status in older adults and improve their micronutrient status to levels associated with reduced risk for several chronic diseases.[27] Nutrient supplementation is often accompanied by an improvement in immune function.[23]

RECOMMENDATIONS FOR RESEARCH

There is a need for research to determine the prevalence of vitamin B_{12} deficiency in our current adult US population, given the prevalence of causative factors reviewed in this article. Additionally, it would be helpful for laboratories to narrow the reference range of serum B_{12} levels, so cases were not overlooked when results are in the low normal range. There is a lack of a gold standard indicator of low B_{12}, presenting a challenge to all investigators of this nutritional problem.[10] Given the sensitivity and specificity of MMA levels for B_{12} deficiency, recommendations of checking this level along with B_{12} and folic acid levels by clinical authorities would be valuable.

We need more studies to confirm that these vitamins have important functions in the etiology of diseases such as Alzheimer's disease, cardiovascular disease, and cancer.[2] We also need to establish if, through improved nutrition earlier in life, these diseases can be prevented or diminished.

Finally, research is needed to demonstrate consistent response to B_{12} supplementation, both in normal and deficient states. Randomized controlled trials are called for to determine the relevance of B_{12} supplementation for the prevention of dementia.[24] The literature is not consistent about recommending exactly how much and how long to supplement B_{12}. JNP

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